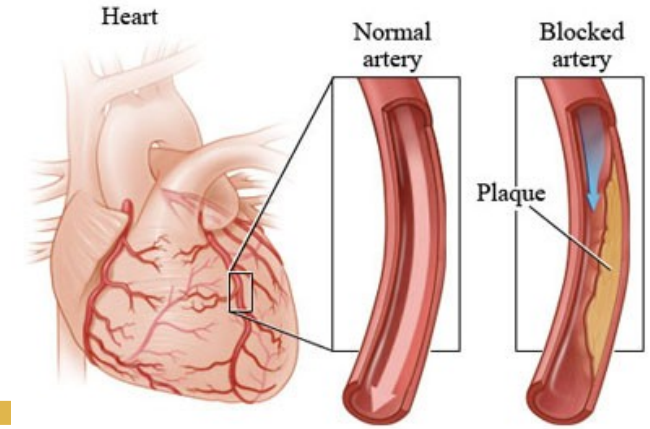




Armed Forces College of Medicine AFCM



Diagnostic Biomarkers of Myocardial Infarction

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Molecular Biology**

INTENDED LEARNING OBJECTIVES (ILO)

By the end of this lecture the student will be able to:

1. Define biomarker of myocardial infarction (MI).
2. List causes and risk factors of MI.
3. Define isoenzymes.
4. Interpret the role of different cardiac biomarkers in diagnosis and follow up of MI.
5. Explain the biochemical basis of streptokinase in treatment of

Case scenario



A 66-year-old man came to the emergency room complaining of heaviness with chest pain radiating to the left shoulder & arm. He is hypertensive, overweight smoker.



Case scenario



He was admitted to the hospital and ECG and echocardiogram (ECHO) were performed. A blood sample was drawn for analysis of serum cardiac biomarkers and lipid profile.

Case scenario



Test results were as follows:

Analyte	Result	Reference range
CK (total)	630 U/L	25-90 U/L
CK (MB)	45 U/L	0-7 U/L
Troponin	3.9 ng/mL	0-0.4 ng/mL
Total cholesterol	420 mg/dL	<200 mg/dL
Triacylglycerol (TAG)	530 mg/dL	<150 mg/dL
HDL-cholesterol	21 mg/dL	34-69 mg/dL
LDL-cholesterol	265 mg/dL	105-180 mg/dL

Case scenario



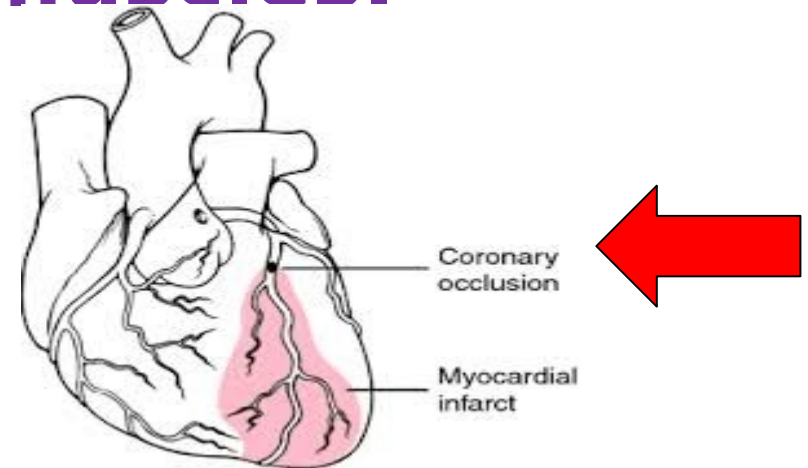
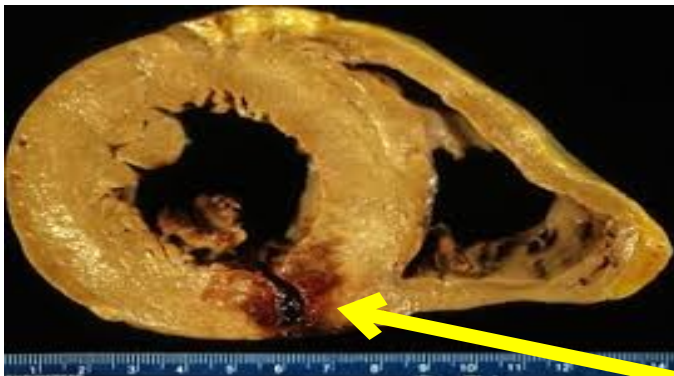
A diagnosis of myocardial infraction (MI) was made. The proper treatment was given, and the doctor advised him to make several lifestyle changes. The doctor also prescribed drugs to lower cholesterol and

What is Myocardial infarction (MI) or Heart Attack?



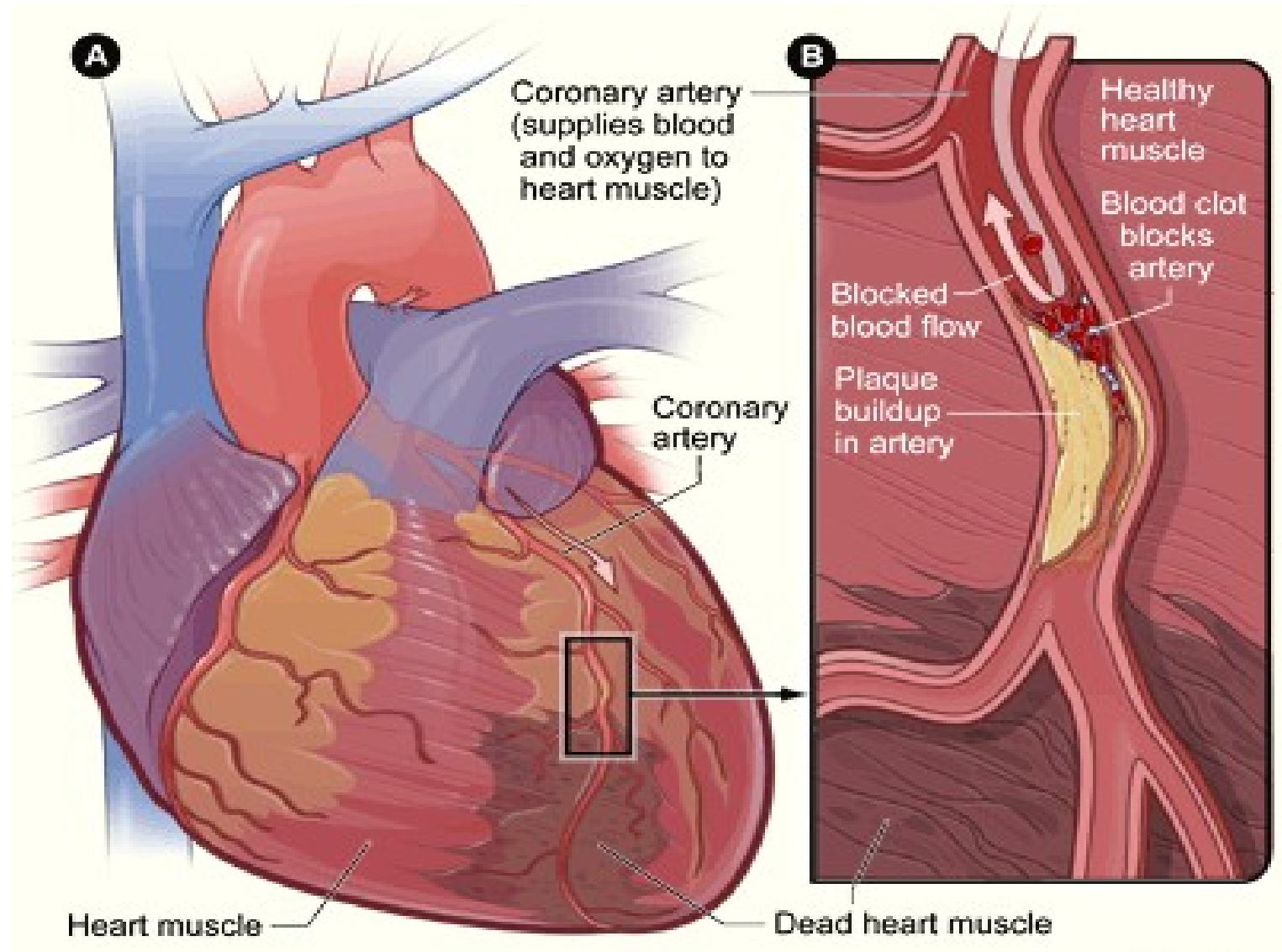
Definition:

Myocardial infarction (MI) occurs when **blood flow stops** to a part of the heart causing **damage & death** of heart muscles.



Causes of MI:

MI occur due to:
coronary artery
occlusion

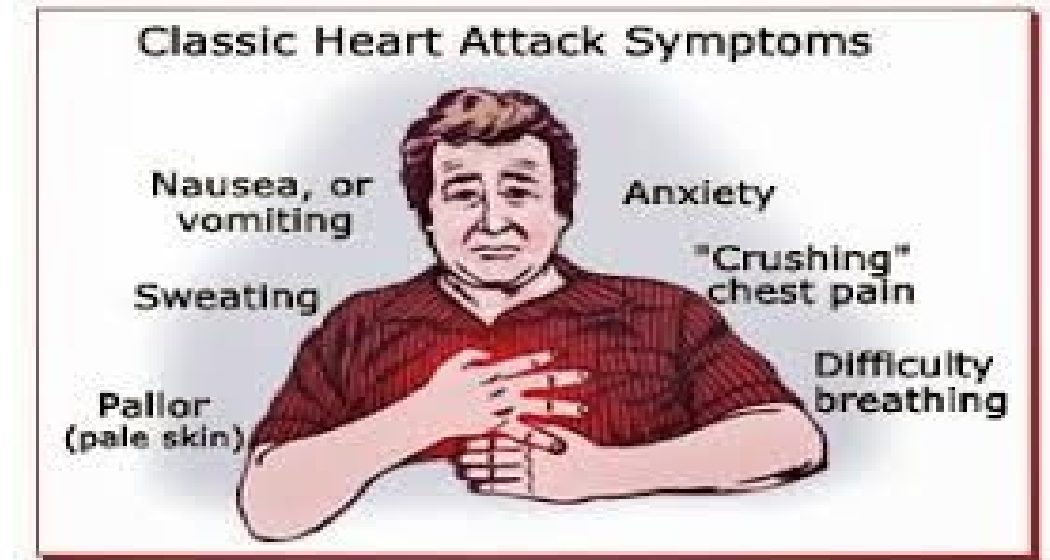


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Symptoms:

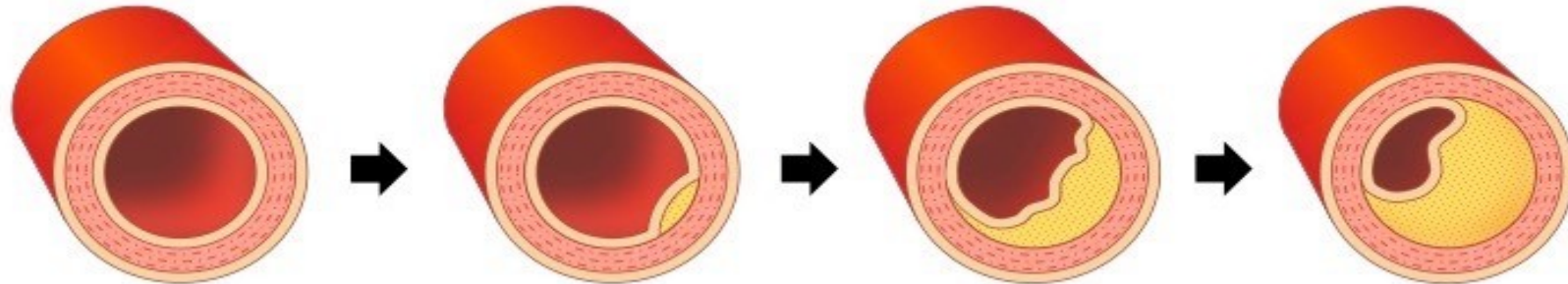
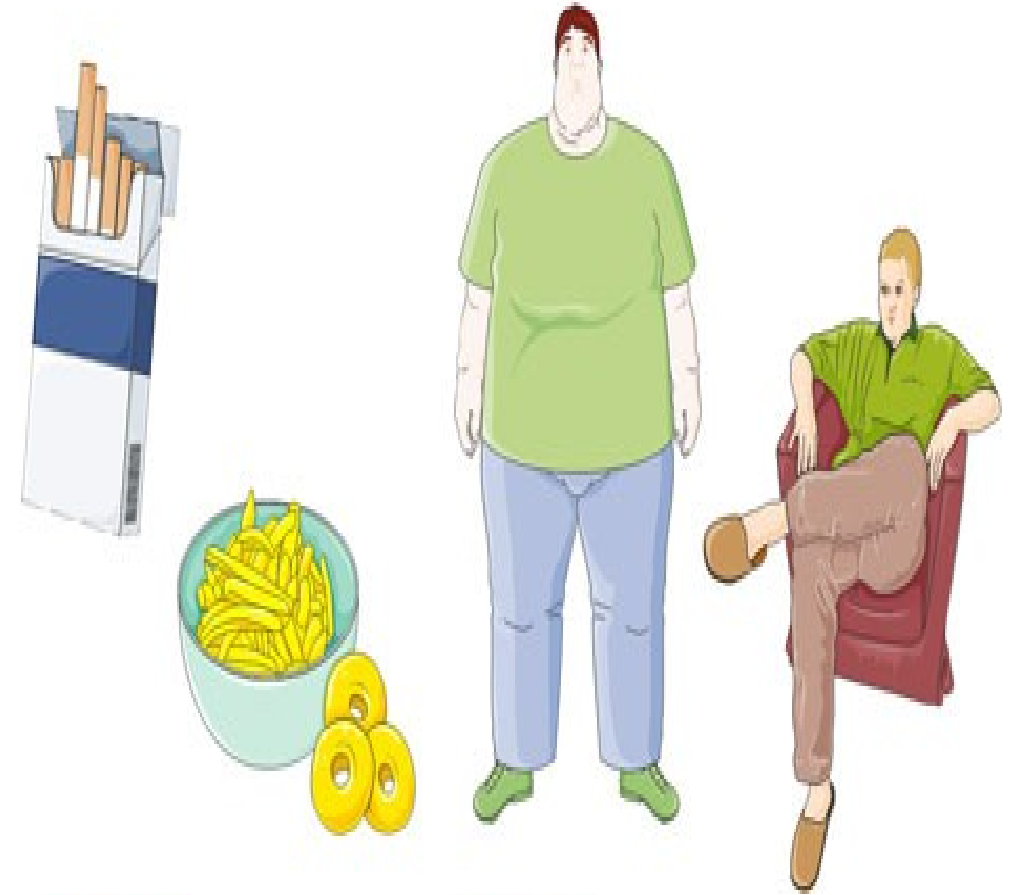
- The most common is **chest pain radiating** to shoulder, arm, back, neck, or jaw.
- Other symptoms may include:

- Shortness of breath
- Nausea
- Fainting



Risk factors of MI:

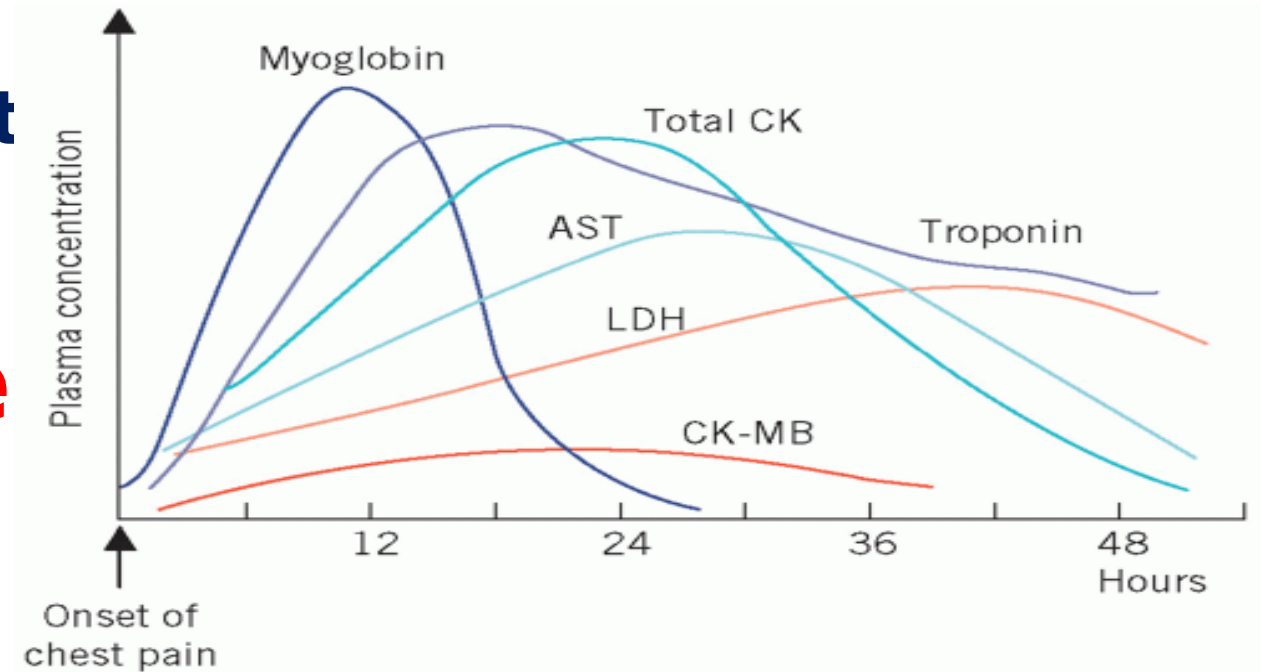
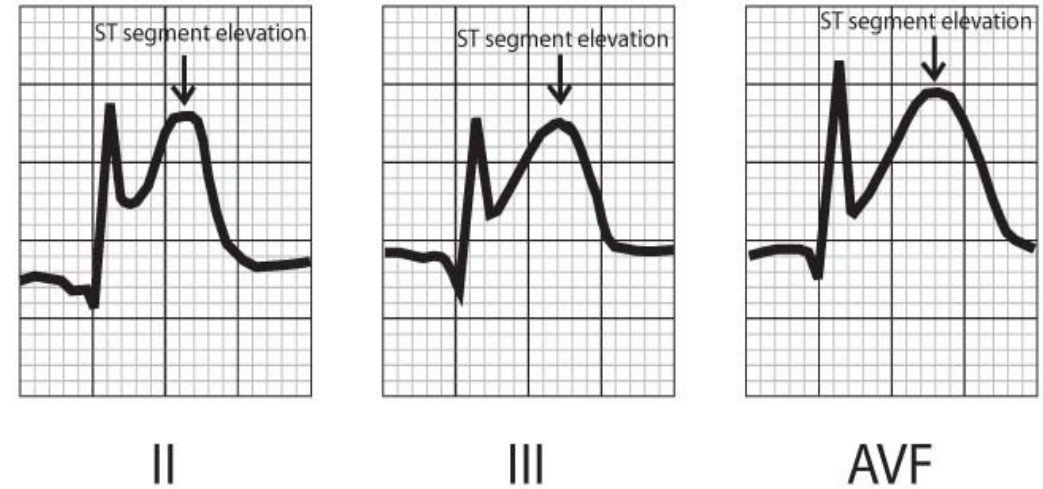
- **High blood pressure**
- **Smoking**
- **Diabetes mellitus**
- **Lack of exercise**
- **Obesity**
- **High blood cholesterol**



Investigations of MI:

- **Electrocardiography (ECG)**
- **Echocardiogram (Echo)**
- **Cholesterol measurement**
- **Cardiac biomarkers**

Acute Inferior Myocardial Infarction



Biomarker



- ✓ A biochemical substance (**protein, enzyme or hormone**) **released** in **sufficient** amount and used as an **indicator** of a certain biological state or **disease**.
- ✓ **Accurately** and repeatedly measured at a reasonable cost.
- ✓ Provide additional information.
- ✓ Aid in **diagnosis, follow-up** and/or **treatment**.

Cardiac biomarkers

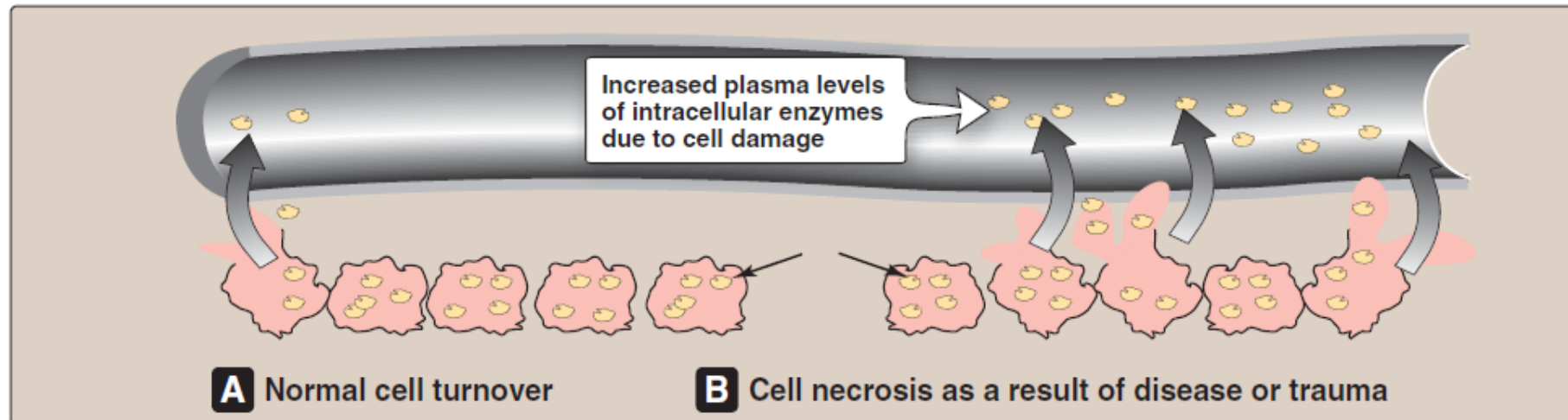


Definition:

Are intracellular proteins (mostly enzymes) specific to the cardiac muscle and released into blood after cell damage. They are used for diagnosis and follow up of MI.

Biochemical changes in MI

Death of cardiomyocytes $\longrightarrow$ **abnormal release**
of these biomarkers (which are normally present
inside the cardiomyocytes) $\longrightarrow$
abnormal increased levels in blood



Cardiac biomarkers



They include:

Isoenzymes

1- Lactate dehydrogenase (LDH)

2- Creatine kinase (CK)

**3- Aspartate aminotransferase
(AST)**

Enzymes

4- Myoglobin

Proteins

5- Cardiac troponins

key question



Which of the following markers is an enzyme?

- A. Troponin**
- B. Myoglobin**
- C. CK**
- D. None of the above**

Isoenzymes



- *Are enzymes that catalyze the same reaction and act on the same Substrate.**
- *Different forms of the same Enzyme.**
- *synthesized in different tissues.**

Isoenzymes



***Differ from each other due to difference in amino acid sequences and number of charged amino acids.**

***Can be separated from each other by ELECTROPHORESIS.**

*** They are made of different subunits**

Isoenzymes



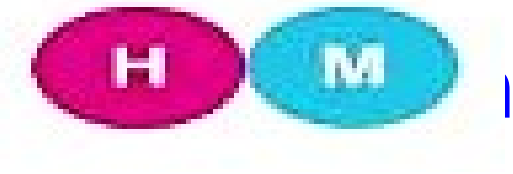
Same

- Catalyze the same reaction
- Act on the same substrate
- Use the same coenzymes

Different

- Subunits
- V_{max} and K_m
- Electrophoretic mobility
- Immunogenic properties
- Heat stability
- Tissues

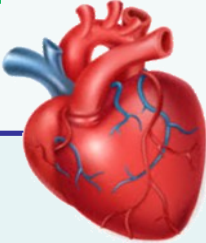
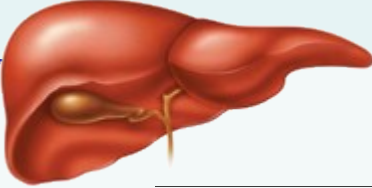
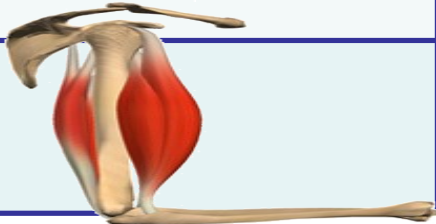
1- Lactate dehydrogenase (LDH)

- LDH is a glycolytic enzyme (anaerobic glycolysis) which catalyzes the conversion of pyruvate to lactate.
- It is an enzyme composed of 4 subunits (tetramer) of H and M 
- They are combined in different ways to give active enzyme.

LDH isoenzymes



Five isoenzymes are present in blood

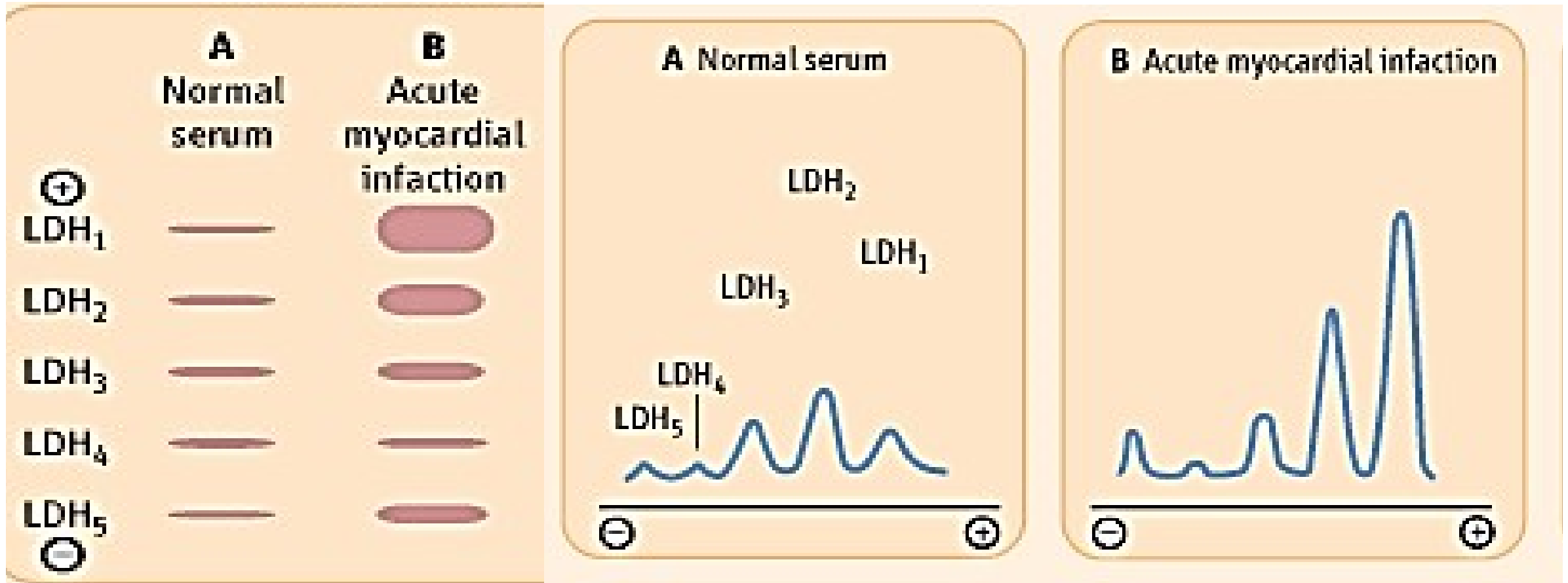
LDH isoenzyme	Tetramer	Specific for
LDH1	HHHH  H ₄ (LDH ₁)	HEART 
LDH2	HHHM  H ₃ M (LDH ₂)	RBCs 
LDH3	HHMM  H ₂ M ₂ (LDH ₃)	BRAIN 
LDH4	HMMM  HM ₃ (LDH ₄)	LIVER 
LDH5	MMMM  M ₄ (LDH ₅)	MUSCLE 

LDH in MI



**The total serum LDH level increases
due to elevation of LDH1 isozyme**

LDH in MI



Disadvantages of LDH

- **Nonspecific:** LDH levels are also high in tissue breakdown or hemolysis. It can mean cancer, meningitis, encephalitis, or HIV.
- **Late marker.**

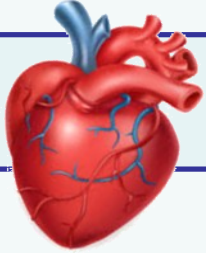
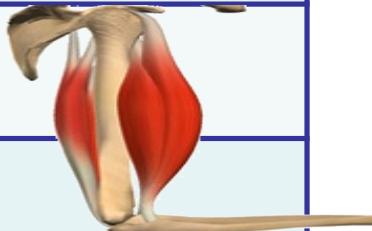


The isoenzymes of lactate dehydrogenase:

- A. can be a monomer or a tetramer**
- B. present only in heart**
- C. exist in five forms, depending upon the content of M and H units**
- D. It is used for early diagnosis of myocardial infarction**

2- Creatine kinase (CK)

- **CK** is an enzyme responsible for transferring a phosphate group from ATP to creatine and plays an important role in **energy storage**.
- It is an enzyme formed of 2 subunits **B** and **M** (**dimer**)

CK isoenzyme	Dimer	Specific for
CK1	BB	BRAIN 
CK2	MB	HEART 
CK3	MM	MUSCLE 

CK in MI



**In myocardial infarction there
is elevation of total CK due to
marked elevation of CK2 (MB)**

3- Aspartate aminotransferase (AST)



- It is enzyme catalyzes the exchange of amino and keto groups between alpha AA & alpha keto acid.
- **Normally, serum AST levels in blood are low.**
- It increases when **liver or heart** is damaged (cell destruction) ☐ more AST release into blood ☐ **increase in blood levels.**
- It is not specific to the heart (**also released by the liver**).

4- Myoglobin



- It is O_2 binding protein in striated & cardiac muscles.
- It has low molecular weight and thus released into circulation after MI.
- An early sensitive marker.
- Nonspecific: increase in skeletal injury & renal failure.

5- Cardiac troponins



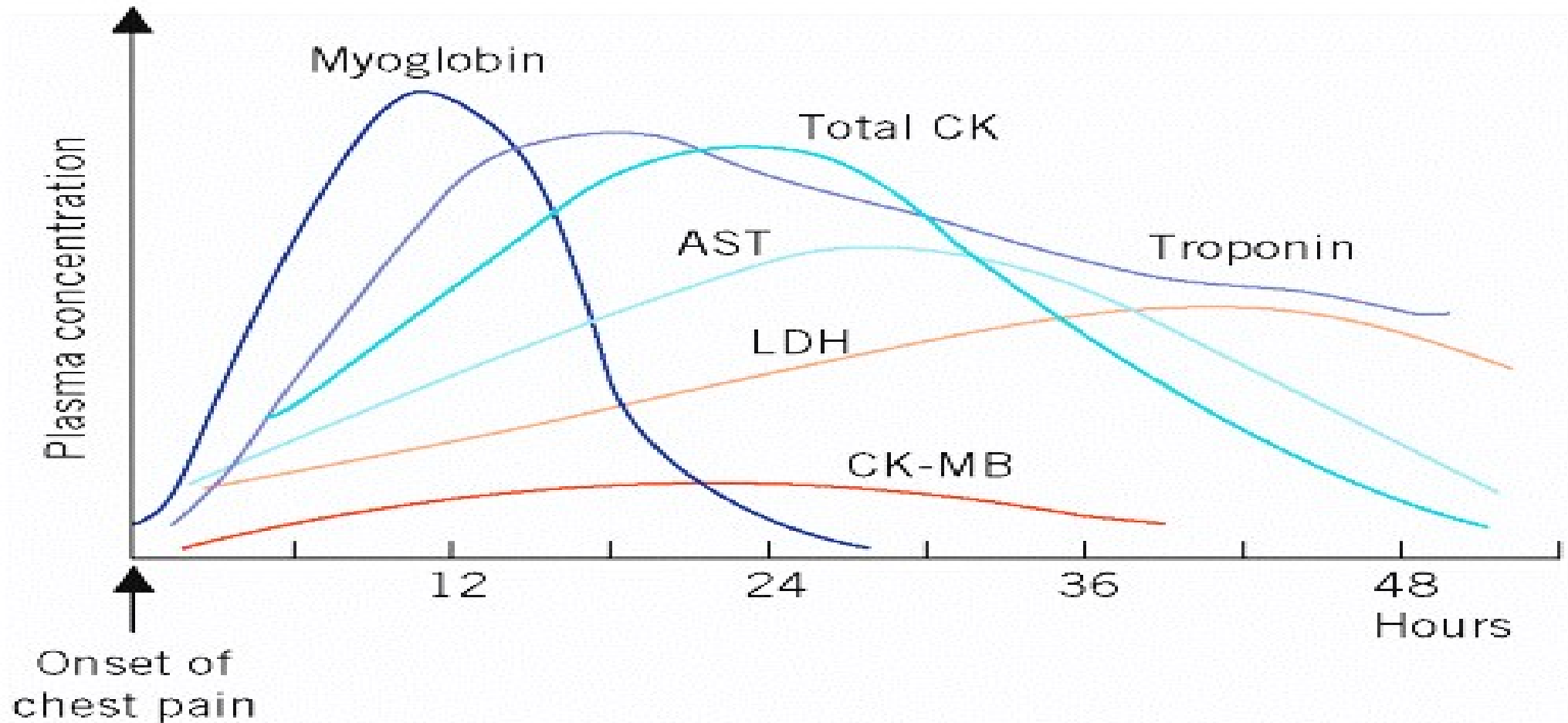
- Troponins are regulatory trimeric proteins (**TnT, TnC, TnI**) of skeletal and cardiac muscles.
- **TnC** of skeletal and cardiac muscles are identical (not used).
- Cardiac troponins (**cTnT & cTnI**) (present within the myocardium) are released into the circulation when damage of cardiomyocyte has occurred (after AMI)

5- Cardiac troponins



- **Serum troponin** is a sensitive marker of myocardial injury and is the most specific.
- It is now considered as the **gold standard** for the diagnosis of MI.

Cardiac biomarkers changes with M_I



Time sequence of cardiac biomarkers changes with MI



Cardiac marker	Rises	Peaks	Returns to normal
Myoglobin	1-2 hours	6-8 hours	1 day
Troponin	1-2 hours	1-2 days	3-5 days (TnI) 5-14 days (TnT)
CK2	4-8 hours	24 hours	2-3 days
LDH1	8-12 hours	3-6 days	8-14 days



In myocardial infarction:

- A. Total LDH is used for diagnosis**
- B. Total CK is used for follow up**
- C. LDH1 is used for early detection**
- D. CK2 is used for early detection**

Cardiac biomarkers changes with MI

- **TnI & CK2** are used for early diagnosis of MI.
- **Myoglobin** is used for as a negative predictor of AMI.
- **TnT & LDH1** are used for follow up of

Ideal biomarker (marker choice)



- **Sensitive** (Myoglobin, Troponin, CK-MB)
- **Specific** (cTnI, cTnT, CK-MB, LDH1)
- **Early released (elevated)** (Myoglobin, cTnI, CK-MB)
- **Stays longer (used for follow-up)** (cTnT & LDH)

Treatment of MI



1. Nitroglycerin: dilate blood vessels

2. Analgesics: like Morphine

3. Aspirin: inhibits platelet aggregation and formation of blood clots

4. Thrombolytic agent (Streptokinase): to break down the blood clots

Streptokinase



- ✓ It is an enzyme used as a therapeutic agent. It is prepared from the bacteria called streptococcus.
- ✓ Used in treatment of MI through ~~pre~~teolytic cleavage of plasminogen ~~→~~ converting it to plasmin turning on the fibrinolytic system lysis of blood clots which cause MI.

✓ Given IV within 90-120 minutes of MI

Streptokinase



Plasminogen

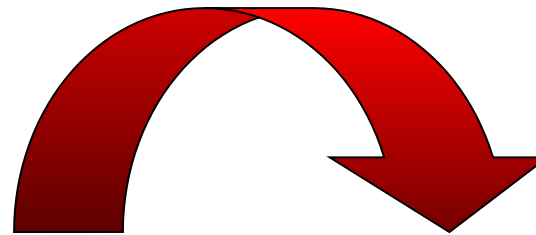
Proteolytic cleavage by
Streptokinase



Plasmin

Cause **Fibrinolysis**

Fibrin



**Fibrin
degradation
product**

key points



- Myocardial infarction (MI) occurs when **blood flow stops** to a part of the heart causing damage & death of heart muscles.
- **Risk factors** for MI include high blood pressure, smoking, diabetes mellitus, lack of exercise, obesity and high blood cholesterol.
- Cardiac biomarkers are **intracellular** proteins (mostly enzymes) specific to the cardiac muscle and **released into blood** after cell damage. They are used for diagnosis and follow-up of MI.

key points



- **Isoenzymes are enzymes that catalyze the same reaction and act on the same substrate. They are different forms of the same enzyme synthesized in different tissues.**
- **TnI & CK2 are used for early diagnosis of MI while TnT & LDH1 is used for follow up.**
- **Streptokinase is an enzyme used in treatment of MI through proteolytic cleavage of plasminogen converting it to plasmin, thus turning on the fibrinolytic system and causing**

SUGGESTED TEXTBOOKS



1. "Lippincott's Illustrated Reviews in Biochemistry" by P.C.Champe, R.A.Harvey and D.R. Ferrier.
2. "Harper's Biochemistry" by R.K.Murray, D.K.Granner, P.A. Mayes and V.W. Rodwell.

Thank You

